haemodynamics are the source of inflammatory and immune activation[6], and that chronic hypoxia may result in endothelial production of free radicals and consequently leukocyte activation[8-10]. The heart itself may be a source of immune activation by this hypothesis. A second asserts that immune activation is a consequence of exposure to exogenous antigen[7].

The clinical problem of end-stage heart failure can be tackled by heart transplantation, and increasingly by the implantation of ventricular assist devices, usually as a bridge to transplantation[23,25]. Problems with devices include thromboembolic events and possible systemic inflammatory responses related to blood contact with artificial surfaces[27]. We have previously shown that the degree of complement activation is a function of the severity of cardiogenic shock prior to circulatory support, rather than an effect of surface activation[28].

In the present study we sought to describe the pattern of inflammatory response to the implantation of a ventricular assist device. The device improves the haemodynamic deficit of severe chronic heart failure, but without removing the heart as a potential source of immune activation. In addition, it adds a potentially potent extra source of immune activation in the shape of an extensive foreign surface. However, if there is significant spillover from cardiac cytokine production, unloading the heart with an assist device should cause long-term reduction in peripheral cytokine levels in survivors.

Despite these potentially potent sources of additional inflammation, and the effects of major surgery, we have found an initial reduction in indices of inflammation as evidenced by a fall in levels of tumour necrosis factor α, interleukin-6 and activated complement. These observations accord with previous work that suggested that left ventricular assist device implantation reduces the expression of myocardial tumour necrosis factor α[29]. Assist device implantation can have a profoundly depressant effect on T-cell function lasting up to 3 months[30]. The fall in tumour necrosis factor α seen with mechanical assist is in contrast to what is seen with medical therapy for acute episodes of decompensation of chronic heart failure where levels do not fall quickly[7,31].

Why is there a gradual increase in indices of immune activation later during the course of the study? There is no sign that the patients are retaining fluid and becoming oedematous again. Equally, with the heart still supported by the assist device, it seems unlikely that the heart has started to secrete tumour necrosis factor α. It may be that there is low grade sepsis that we have not detected clinically, or it may reflect immunosuppression induced by surgery and illness, that is then subsequently wearing off. Inflammatory and immune activation may be independent of haemodynamic and functional changes.

We found no fall in the levels of CD14 and soluble tumour necrosis factor receptor; indeed there was a slight rise in CD14 over the period of the study. CD14 is thought to be representative of longer term exposure to endotoxin. The temporary fall in tumour necrosis factor α and interleukin-6 might be explained by a short-term reduction in ischaemia as a result of an increase in cardiac output. In the longer term, tumour necrosis factor α increases again (and other inflammatory markers never change) because the pathophysiological process resulting in inflammation is not altered by assist device implantation, as suggested by the persisting CD14 level.

We considered the possibility that changes in plasma volume might influence cytokine levels, but we saw no change in haemoglobin or haematocrit (which was influenced by surgical management). Therefore we believe that plasma volume could only have had a minor influence. Nevertheless, the volume of distribution of cytokines in heart failure patients is not known. In view of the loss of weight in the first week after surgery, this may have influenced results; future studies will have to address this issue in detail.

Cardiopulmonary bypass circuits have been shown to be potent stimulants of an inflammatory response in the short-term[32,33], but we saw a fall in activated complement and elastase at 1 week. This is perhaps surprising in view of the pro-thrombotic stimulus represented by the support device. It might be that the stress of illness and surgery resulted in suppression of the immune response[34]. Nevertheless, complement levels were higher than seen in normal subjects (C3a $<200\,ng.ml^{-1}$, C5a $<500\,ng.ml^{-1}$). Elastase was reduced to within the normal range ($<85\,\mu g.ml^{-1}$).

There is no currently available treatment specifically for increasing body weight in heart failure patients. Restoring cardiac output might have such an effect. We observed significant weight loss after the assist devices were implanted (6·5 kg, or 8·1% of body mass). This weight loss is probably due, at least in part, to reductions in body oedema, although we were not able specifically to test for this. It might be thought that greater pre-operative weight represents more fluid retention, and hence worse heart failure, but in this group of patients, a higher pre-operative weight conferred a better prognosis. This may reflect the known adverse effect of cachexia on prognosis[3]. The left ventricular assist device implantation did not seem to function as a specific anticachexia intervention, as suggested by the fact that there was a further (small) decline in body mass index by the 90 day follow-up.

Limitations

There is a possible confounder in the tumour necrosis factor α data in that the administration of heparin can enhance tumour necrosis factor production by monocytes[35]. All our patients were still receiving heparin at the 1 week time point, suggesting that the intrinsic fall in tumour necrosis factor α may be being under-estimated. Monocytes are the main site of tumour necrosis factor α production and we have not measured differential white cell counts, nor have we measured left ventricular volumes, and cannot thus assess any effect that change in wall stress may have on immune activation.

Conclusions

Patients undergoing ventricular assist device implantation for severe congestive heart failure as a bridge to transplantation have evidence of inflammatory activation as demonstrated by raised levels of tumour necrosis factor α and its receptor, activated complement and elastase and CD14. The levels of tumour necrosis factor α, interleukin-6, C3a and elastase are all reduced by device implantation, although levels start to rise again between 1 week and 1 month after operation. In the short-term in this group of severely diseased patients, left ventricular assist device implantation has no anti-cachectic effect. Lower body mass index at the time of device implantation is a powerful predictor of poor outcome.

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